REMARKS

Claims 20-24 are pending examination in this application, of which claim 20 is independent. Claim 23 has been amended to correct an inadvertent typographical error by substituting "1000" with --10000--. Support for this amendment can be found throughout the specification, for example, in original claim 1. New claim 24 has been added, support for which can be found in Example 1 at page 7 of the specification. Applicants respectfully submit that no new matter will be introduced into the application upon entry of these amendments to the claims.

Applicants' agent submitted amended claim 23 in a supplemental response forwarded to the USPTO via facsimile on January 11, 2002, but no reference was made to this supplemental response in the outstanding Office Action. To ensure the typographical error is corrected, Applicants' agent is submitting amended claim 23 once again out of an abundance of caution. Entry and consideration are respectfully requested.

Claims 20-23 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Wolf et al (DD 411996, hereinafter "DD '996") taken with Behre et al (1992, hereinafter "Behre"), Reissmann et al (1994, hereinafter "Reissmann") and Diedrich et al (1994, hereinafter "Diedrich"). This rejection is respectfully traversed for at least the following reasons.

Two of the cited references, i.e. Reissmann and Diedrich, do not constitute prior art for the subject application within the meaning of the 35 U.S.C. § 102. The publication dates of both referenced articles is May of 1994. The present application claims benefit of priority under 35 U.S.C. §119 from German Application No. P4305225.8, having a filing date of February 19, 1993. Furthermore the present

application claims benefit of an earlier filing date under 35 U.S.C. §120 from the parent application No. 08/198,037, filed on February 22, 1994. Therefore, it is submitted that the cited references can not be validly used as prior art references in rejection of the claims of the instant application. Therefore, Applicants will only address the rejection of the claims in view of DD '998 taken with Behre.

DD '998 discloses a method for the production of lyophilized LHRH preparations in which LHRH means the decapeptide having the formula:

Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2

DD'998 describes a method for the production of a lyophilized form of this decapeptide requiring the addition of acetic acid and mannitol. Such preparations are undertaken, according to the reference, "to improve the quality and stability of parenterally applicable LHRH preparations". *See* DD '998 at page 4. DD '998 employs buffering agents to reach a preparation pH of 3.5 –6.5 prior to lyophilization to achieve improved storage stability. *See* DD '998 at page 4.

By contrast, the claims are directed to a method of preparing a sterile Cetrorelix lyophilizate, which has the decapeptide formula:

AC-D-Nal92)-D-pCl-Phe-D-Pal(3)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2

Aqueous solutions of this decapeptide are unstable, particularly during heat sterilization processes. *See* instant specification at page 1. Skilled artisans know that oligopeptides, particularly those with terminal amides, tend to form gels that substantially impair the filterability of such peptides. *See* instant specification at page 3. In order to overcome this sterilization problem, Applicants discovered that Cetrorelix may be dissolved in 30% volume/volume acetic acid to form a solution,

which is then diluted to achieve a final strength of 3%. Such 3% solutions can be sterile filtered without unacceptable loss of material. *See* instant specification at page 4. The stability of Cetrorelix in the 30% (W/W) acetic acid solution was unexpected.

Claim 20 recites a method comprising the steps of dissolving Cetrorelix in aqueous acetic acid to form a solution, and then diluting the solution with water for injection. Bulking agent is then added to the solution, and the solution is sterile filtered for dispensing into injection vials and lyophilized.

Claim 23 further defines the preparation of a solution in which Cetrorelix acetate is dissolved in 100-10,000 parts by weight of a 30% strength (W/W) acetic acid solution, which is further diluted with water to achieve 3% strength aqueous acetic acid.

Claim 24 further defines the 3% solution as exhibiting a pH value between 2.5-3.0.

DD '998 fails to teach the claimed method, as this reference requires the addition of buffering agents to maintain lyophilizate stability of the decapeptide disclosed therein. The claimed embodiments of the invention do not employ buffering agents. The pH of the DD '998 solutions is adjusted to a range of 3.5 to 6.5, which is outside the claimed range. Moreover, DD '998 is silent with respect to avoiding loss of peptide during filtration, and fails to recognize the importance of dissolving decapeptides having terminal amide functions in aqueous acetic acid to form a solution, and then diluting the solution with water for injection to avoid retention of the peptide in filters.

Behre does not overcome the deficiencies of DD '998. Behre teaches that Cetrorelix is an antagonistic analog of GnRH having the potential for use in the

treatment of sex hormone-dependent diseases and male contraception. The Examiner points out that this reference discloses lyophilized Cetrorelix is dissolved in water containing mannitol for injection.

However, the claims are directed to methods of preparing a sterile Cetrorelix lyophilizate, not a method of reconstituting lyophilized Cetrorelix. Behre is silent with respect to improving the filterability of Cetrorelix solutions, and does not teach the dissolution of decapeptides having terminal amide functions in aqueous acetic acid to form a solution, and then diluting the solution with water for injection to avoid retention of the peptide in filters. Accordingly, Behre fails to supplement the deficiencies of DD '998.

For the reasons given above, the combination of DD '998 with Behre does not teach the claimed embodiments of the invention. Applicants respectfully submit that the Section 103-based rejection in view of DD '998 and the secondary reference Behre should be withdrawn.

In view of the foregoing amendment and remarks, Applicants respectfully submit that this application is in condition for allowance. Notification to that effect is earnestly solicited. Should questions relating to patentability arise, the Examiner is invited to telephone the undersigned to discuss the same.

Respectfully submitted,

PILLSBURY WINTHROP, LLP

By _____ 37,087
Blair Elizabeth Taylor, Ph.D.
Reg. No. 44,370
Tel: (703) 905-2198
Fax: (703) 905-2500

1600 Tysons Boulevard
McLean, Virginia 22102
Enclosure: Appendix

APPENDIX
MARK UP VERSION SHOWING CHANGES MADE

The application has been amended as shown below.

IN THE CLAIMS:

The claims have been amended as indicated.

23. (Four Times Amended) The method according to claim 20,

wherein 1 part by weight of cetrorelix acetate is dissolved in 100 – **[1000]** 10,000 parts by weight of a 30% strength (w/w) acetic acid solution and diluted with water to 3% strength aqueous acetic acid, and

wherein the bulking agent is mannitol.